Reactivity of Stable Trifluoroacetaldehyde Hemiaminals. 2. Generation and Synthetic Potentialities of Fluorinated Iminiums

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Under Lewis acid activation, hemiaminals of trifluoroacetaldehyde and related (fluoroalkyl)-aldehydes generate iminium species that can react with various nucleophiles to provide fluorinated amines.

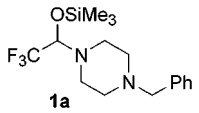
Interest in fluorine-containing compounds is continuously growing[1] since fluorinated organic products present unique properties[2] that are of great interest for a variety of applications[3−5] and, in particular, for the design of bioactive compounds.[3] Thus, because of this tremendous interest, research for new methodologies to prepare fluorinated compounds, by the shortest route, is still a challenge.

Generally speaking, synthetic routes involving iminiums species are useful strategies for amino compound functionalization.[6] Following this concept, Fuchigami et al.[7−9] and Dolbier et al.[10] have demonstrated the effectiveness of trapping in situ generated trifluoromethylated iminiums by various nucleophiles. However, the trifluoroacetaldehyde *N*,*O*-acetals[7−9] or *N*,*N*-aminals[10] they used suffer from a difficult access and a lack of variety in amino moieties.

We have recently shown that the easy accessible (even on a multigram scale[11]) silylated hemiaminal of trifluoroacetaldehyde **1a** (Chart 1) is a very efficient precursor of the corresponding iminium salt under Lewis acid activation.[12]

Furthermore, a lot of bioactive substances bearing a piperazino group[13] are described in the literature, and several of them led to commercial drugs.[14] Thus, we focused our interest on the use of our iminium strategy for the synthesis of fluorinated compound bearing a piperazino moiety and studied the reactivity of **1**, under Lewis acid activation, toward various nucleophiles. The first ones we envisaged were heteronucleophiles as alcohols and amines (Table 1).

Chart 1. Silylated Hemiaminal of Fluoral



1a

This reaction generally provides satisfactory yields which, however, are lower with secondary alcohols (Table 1, entry 3) because they are probably more sensitive to Lewis acids and lead to side reactions. Such side reactions are especially important with sugar derivatives (Table 1, entry 5) that are poly-oxygenated reagents. Indeed, under usual conditions (see the Experimental Section), no **2ae** was obtained, but this target substrate can be successfully synthesized when **1a** is prechelated with the Lewis acid before introduction of the carbohydrate. Tertiary alcohols have not been tested because of their high sensitivity toward Lewis acids.

This strategy provides more elaborated *N*,*O*-acetals of fluoral than previously described and constitutes the unique possibility to reach such compounds since the standard O-alkylation of fluoral hemiaminolate under basic conditions failed in our hands.

As we previously described the preparation of other fluorinated hemiaminals,[12] they were reacted in the same way to deliver the corresponding *N*,*O*-acetals (Table 1, entries 6 and 7).

The reaction with sulfur-centered nucleophiles is under study in our laboratory and will be reported in due course.

Then, to create C−C bonds, we turned our attention to carbon nucleophiles. However, carbon-centered anions, like Grignard's reagents or organolithium derivatives, failed to give the expected products, certainly because of their high affinity toward Lewis acid. To circumvent this disappointing result, neutral carbon nucleophiles were engaged. In this respect, allylsilane was very efficient and provided fluoroalkylated homoallylic amines at room temperature (Table 2).

(1) Schofield, H. *J. Fluorine Chem.* **1999**, *100*, 7−11.
(2) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3−11.
(3) Filler, R.; Kobayashi, Y.; Yagulpolskii, Y. L. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, 1993.
(4) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994.
(5) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II. A critical Review*; ACS Monograph 187; American Chemical Society: Washington, DC, 1995.
(6) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.
(7) Fuchigami, T.; Ichikawa, S.; Konno, A.; Nonaka, T. *Chem. Lett.* **1989**, 1987−1988.
(8) Fuchigami, T.; Ichikawa, S.; Kandeel, Z. E.; Konno, A.; Nonaka, T. *Heterocycles* **1990**, *31*, 415−417.
(9) Fuchigami, T.; Ichikawa, S. *J. Org. Chem.* **1994**, *59*, 607−615.
(10) Xu, Y.; Dolbier, W. R., Jr. *J. Org. Chem.* **2000**, *65*, 2134−2137.
(11) Billard, T.; Langlois, B. R.; Blond, G. *Tetrahedron Lett.* **2000**, *41*, 8777−8780.
(12) Blond, G.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2001**, *66*, 4826−4830.
(13) *The Merk Index*, 12th ed.; Merck & Co., Inc.: Rahway, NJ, 1996.
(14) *Index Nominum: International drug directory*, 16th ed.; Swiss Pharmaceutical Society, Ed.; MedPharm Scientific Publishers: Stuttgart, 1995.

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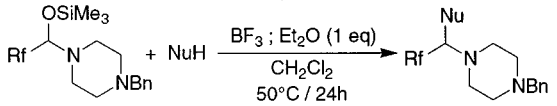
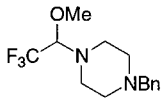
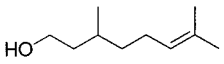
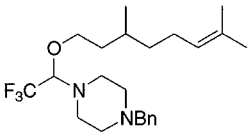
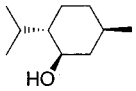
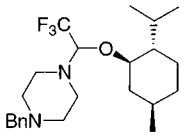
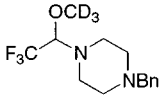
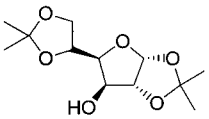
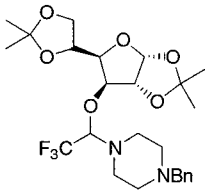
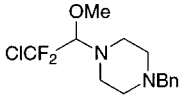
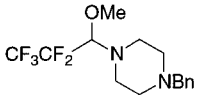
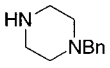
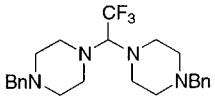
Table 1. Reaction of Fluoroalkylated Iminiums with Alcohols and Amines



1a : Rf = CF_3
1b : Rf = $ClCF_2$
1c : Rf = CF_3CF_2

2

Entry	Hemiaminal	NuH	2 (%)[a]
1	**1a**	MeOH	 **2aa** (80)
2	**1a**		 **2ab** (65)
3	**1a**		 **2ac** (58)
4	**1a**	CD_3OD	 **2ad** (70)
5	**1a**		 **2ae** (40)
6	**1b**	MeOH	 **2ba** (80)
7	**1c**	MeOH	 **2ca** (76)
8	**1a**		 **2af** (65)

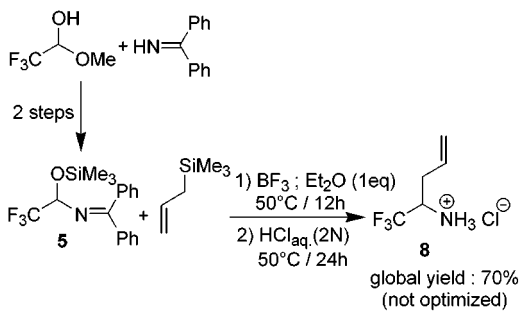
[a] Isolated yield.

This reaction delivered good yields and was applied, as above, to hemiaminals of different fluoroaldehydes (R_F = CF_3, $ClCF_2$, C_2F_5). As such, hemiaminals also can be produced from various amines; this strategy was extended to the preparation of different homoallylic amines. In particular, the derivative of benzophenone imine **5** (Table 2, entry 5) is very interesting because **7** can be deprotected to provide primary α-trifluoromethyl homoallylic amines. It is noteworthy that allylation and deprotection can be carried out in the same pot (Scheme 1).

Such an allylation reaction can also be carried out with allyl-*n*-tributyltin instead of allyltrimethylsilane (Scheme 2), but the presence of tin makes purification more tricky.

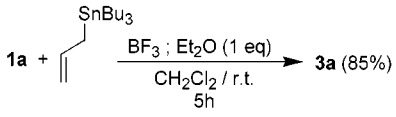
In contrast, vinylsilanes failed to deliver α-fluoroalkylated allylamines, but under the conditions used for allylsilane, potassium styryltrifluoroborates did (Scheme 3).

Scheme 1. One-Pot Synthesis of α-Trifluoromethylhomoallylic Amine

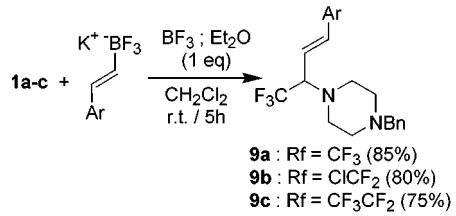


Concerning the mechanism of this reaction, two hypotheses can be formulated. First, boron trifluoride activates the hemiaminal to form an iminium species that then reacts with styryltrifluoroborate to deliver the

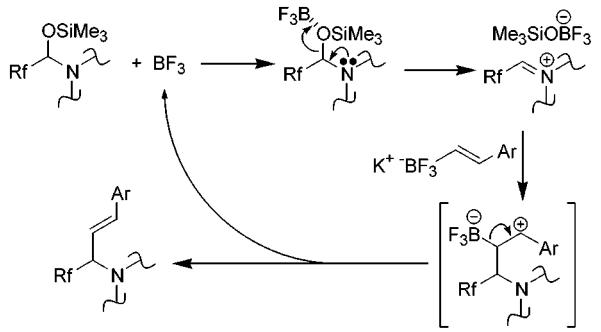
Scheme 2. Allylation of Trifluoromethylated Iminiums with Allyltributyltin



Scheme 3. Vinylation of Fluorinated Iminiums



Scheme 4. First Mechanism of Vinylation



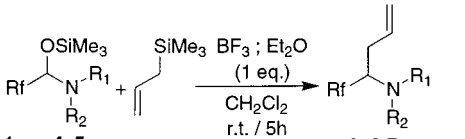
expected product and regenerate boron trifluoride; in this case, the Lewis acid could be used in a catalytic amount (Scheme 4). Second, BF_3·Et_2O reacts first with styryltrifluoroborate to provide, as described by Kaufmann et al.,[15] styrylboron difluoride, which is also a Lewis acid[16] able to activate the hemiaminal and generate iminium and nucleophilic species (Scheme 5). In this second case, BF_3 could not be used in a catalytic amount.

Indeed, when the reaction was carried out with a catalytic amount of BF_3·Et_2O (10% mol), around 10% of the expected product was obtained. Furthermore, when the reaction was monitored by ^{11}B NMR, styrylboron difluoride (δ = 23 ppm)[17] was detected. These experimental observations led us to postulate that the second mechanism is the most probable.

Continuing our search for C−C bond formation, we then examined the electrophilic substitution of electron-rich aromatic compounds with **1a**−**c** (Scheme 6).

Finally, this iminium strategy was applied to other miscellaneous silicon-containing nucleophiles in order to extend its scope (Table 3).

Table 2. Reaction of Fluorinated Iminiums with Allylsilane



Entry	Hemiaminal	3, 6-7 (%)
1	**1a**	**3a** (87)
2	**1b**	**3b** (86)
3	**1c**	**3c** (77)
4	**4**	**6** (76)
5	**5**	**7** (60)[a]

[a] After heating at 50 °C for 12 h.

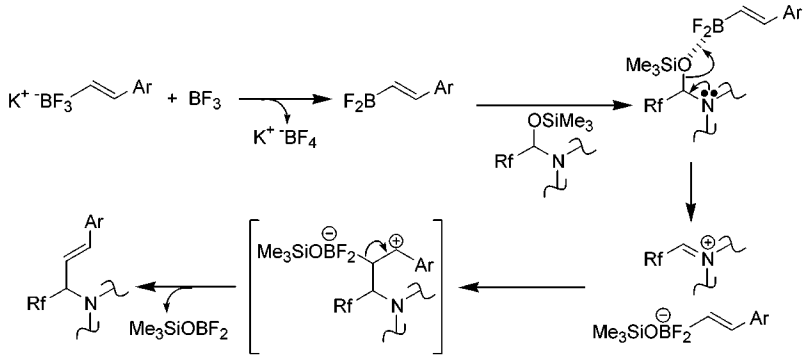
All these reactions provide a very easy access to various α-functionalized fluoroalkylated amines. Nevertheless, no stereoselectivity was observed since reagents **1a**−**c**, **4**, and **5** were racemic in nature.

To circumvent that, we tried to induce diastereoselectivity by using an optically pure hemiaminal. Such a compound has been prepared starting from ephedrine, following the strategy of Mikami et al.[18] (Scheme 7).

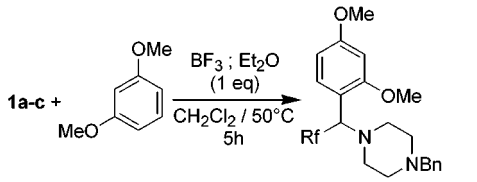
The resulting trifluoromethylated oxazolidine **13** reacted under usual conditions with allylsilane to give **14** with a high diastereoselective excess but in a moderate yield.

It can be noticed that, during the progress of this study, Brigaud et al. presented a similar work using various amino alcohols for the oxazolidine synthesis and different silylated nucleophiles for the second step.[19]

Scheme 5. Second Mechanism of Vinylation

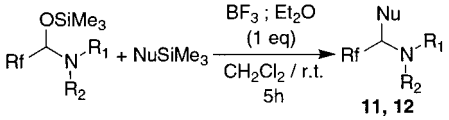


Scheme 6. Friedel–Crafts Reaction with Fluorinated Iminiums

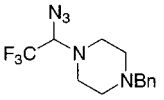
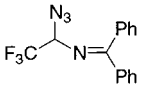
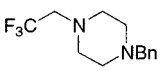
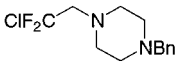
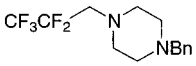
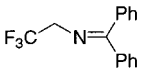


10a : Rf = CF_3 (70%)
10b : Rf = $ClCF_2$ (70%)
10c : Rf = CF_3CF_2 (55%)

Table 3. Reaction of Fluorinated Iminiums with Miscellaneous Nucleophiles



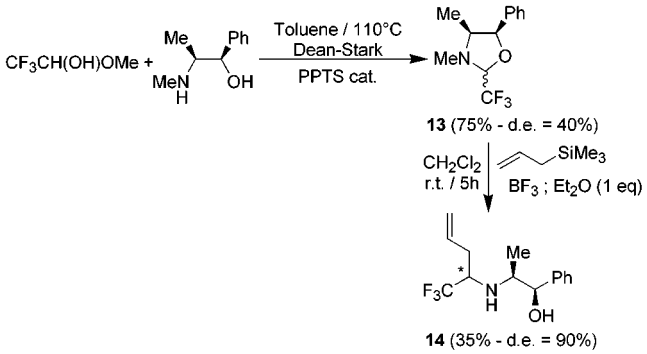
11, 12

Entry	Reagent	$NuSiMe_3$	**11, 12** (%)
1	**1a**	N_3SiMe_3	 **11a** (87)
2	**5**	N_3SiMe_3	 **11d** (70)[a]
3	**1a**	$HSiEt_3$	 **12a** (85)
4	**1b**	$HSiEt_3$	 **12b** (80)
5	**1c**	$HSiEt_3$	 **12c** (84)
6	**5**	$HSiEt_3$	 **12d** (61)[a]

[a] After heating at 50 °C for 24 h.

In conclusion, we have shown that hemiaminals of fluoroalkylaldehydes are very efficient precursors of fluoroalkylated iminium species that can be trapped by various nucleophiles to provide α-substituted α-(fluoroalkyl)amines. Their use for targeted synthetic applications is under study in our laboratory.

Scheme 7. Stereoselective Access to α-Trifluoromethyl Homoallylic Amines



Experimental Section

General Remarks. Solvents were distilled prior to use. Other reagents were used as received. Flash chromatography was performed on silica gel 60 M (0.04–0.063 mm). Reagents **1a–c** and **4** were prepared according to our previous work.[11,12] Hemiaminal **5** were prepared with the same procedures.

Typical Procedure. $BF_3{\cdot}Et_2O$ (1 mmol) was added, at room temperature, to a solution of **1a–c**, **4**, or **5** (1 mmol) and the nucleophile (1 mmol) in CH_2Cl_2 (1 mL). Then, the mixture was stirred at the temperature and for the time indicated in the text. At the end of the reaction, *N*-methylethanolamine was added to complex boron byproducts, and the crude mixture was stirred for 1 h.Then, it was deposited at the top of a silica gel column and eluted.

Acknowledgment. The CNRS is thanked for financial support.

Supporting Information Available: Characterization data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016265T

(15) Bir, G.; Schacht, W.; Kaufmann, D. *J. Organomet. Chem.* **1988**, *340*, 267–271.

(16) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027.

(17) This ^{11}B NMR shift was close to the one described in ref 15. When the reaction is monitored by ^{1}B NMR, a new peak appears at 14.3 ppm, which could be attributed to Me_3SiOBF_2. However, attempts to isolate this compound failed.

(18) Ishii, A.; Higashiyama, K.; Mikami, K. *Synlett* **1997**, 1381–1382.

(19) Brigaud, T.; Lebouvier, N. *Abstracts of Papers*, 13th European Symposium on Fluorine Chemistry, 15–20 July 2001, Bordeaux, France; Abstract 2-P29.